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to Recent Hypotheses con-
cerning the Transmission of
Malaria.

BY

THEOBALD SMITH, M. D.,

George Fabyan Professor of Comparative Pathology in the
Medical Department of Harvard University; Pathologist
to the State Board of Health of Massachusetts.

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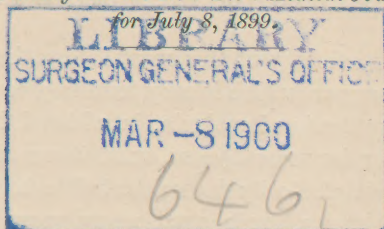
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THE
ÆTIOLOGY OF TEXAS CATTLE FEVER,
WITH SPECIAL REFERENCE
TO RECENT HYPOTHESES CONCERNING THE
TRANSMISSION OF MALARIA.*

By THEOBALD SMITH, M. D.,

GEORGE FABYAN PROFESSOR OF COMPARATIVE PATHOLOGY
IN THE MEDICAL DEPARTMENT OF HARVARD UNIVERSITY;
PATHOLOGIST TO THE STATE BOARD OF HEALTH OF MASSACHUSETTS.

THE studies upon human and animal diseases carried on recently by Koch in the heart of Africa, and his enunciation of an hypothesis concerning the transmission of malaria by stinging insects, more particularly by mosquitoes, have drawn attention to the ætiology of Texas cattle fever, upon which his hypothesis was based. Our studies on Texas fever have been so fully recorded † that the only excuse I have in accepting the invitation of your president to bring out once again the salient

* Read before the New York Academy of Medicine, April 6, 1899.

† Theobald Smith and F. L. Kilborne. *Investigations into the Nature, Causation, and Prevention of Southern Cattle Fever*, Washington, 1893, pp. 304. For an abridged reprint, see the *Eighth and Ninth Annual Reports of the Bureau of Animal Industry* (1891, 1892). A brief summary by the writer may be found in *Centralblatt f. Bacteriologie*, vol. xiii, 1893, p. 511, and some additional data in *Transactions of the Association of American Physicians* for 1893.

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facts in the ætiology of this most interesting disease is the moral support which it may tend to give to the inoculation hypothesis of malaria, in which I have been a firm believer for several years, until it can either be disproved or satisfactorily demonstrated to be true.

It was known for a good many years by farmers and agriculturists of the United States that healthy cattle driven north beyond a certain line during the warm season of the year would infect pastures with a virus highly fatal to the native cattle grazing on them.

When in 1868 the early slow process of driving cattle afoot was abandoned, and the steamboat and the railroad were substituted, this peculiar disease was disseminated over a wide territory, even reaching this city. It was also known that cattle driven south from the northern side of this line contracted the same disease. The investigations of Dr. D. E. Salmon during the years 1880-'84 defined more accurately this line, and showed the existence of a large permanently infected territory, including most of the Southern States. At present the National Government issues annually rules and regulations governing the movement of the cattle from this enzootic territory, so as to protect the live-stock interests of the North. But even now the rules are sometimes broken, and in 1897 this disease appeared in a number of cows about Boston. The virus had been dropped in the Albany stock yards, and from there taken to those near Boston. The line, as drawn at present by the Department of Agriculture, meanders across the country between the twenty-ninth and forty-second parallels of latitude.

The importance of knowing something of the mysterious agencies of this disease led the government

and some of the States to induce a number of persons to investigate it. Beginning with 1868, various reports have been issued, the most satisfactory of these being one by R. C. Stiles on investigations made in this city in 1868 for the then Metropolitan Board of Health. Its only disfigurement is the part added by Ernst Hællier, of Jena, on the ætiology, which serves well to illustrate the vagaries of pseudo-science. Of the other reports dealing with the ætiology, the less is said the better. They can be resurrected by any one so desiring, by consulting the references in our full report.

In 1888 I was first introduced to this subject by examining portions of the organs of animals which had succumbed to it in Maryland and Virginia. These were brought to the laboratory at Washington on ice. At this time the only report which pretended to make any detailed statements concerning the lesions produced by Texas fever was the one by R. C. Stiles. It was therefore necessary to study the subject from the bottom to get some data on which to found the ætiological work. From the pieces examined in the summer of 1888 I became convinced that a corpuscle-destroying parasite was at work. Laveran's discovery and subsequent researches by Italian writers, more particularly Golgi, had paved the way for this assumption. The material was not in any satisfactory condition for studies of the blood, and this part of the work was postponed until the blood of a living animal could be examined. In the meantime appeared Babès's work on the hæmoglobinuria of cattle in Roumania.* Babès found in this disease a coccus within the red corpuscles, which he cultivated, though with difficulty, and passed through

* *Archiv f. pathol. Anatomie*, vol. cxv, 1889, p. 81.

several rabbits. Subsequent events showed that he saw the true parasite, but went astray in assuming that it was a bacterium, and in cultivating some other organism, possibly that of rabbit septicæmia. He regarded the drinking troughs as disseminators of the disease. Since his first communication Babès has gradually converted his diplococcus into a protozoan parasite, and has reported the presence of ticks upon Roumanian cattle. Through the efforts of Dr. Salmon, chief of the Bureau of Animal Industry, my wish to have diseased animals within easy reach of the laboratory was carried out in the summer of 1889, and the very first cases revealed the intraglobular parasite.* It was only necessary now to interpret certain peculiar appearances of the blood-corpuscles, due to the extreme anæmia,† which might have been taken for stages in the life history of the parasite, and we had a ready means of diagnosis. The microscope and Thoma's blood-corpuscle counter, aided by the clinical thermometer, were thereafter the chief means of recognizing the disease. The work accomplished in the summer of 1889 furnished us with certain data concerning the pathology of Texas fever and the micro-organism to which I shall very briefly allude before taking up the mechanism of its transmission.

The acute type of the disease begins with a high fever, reaching not infrequently 107° and 108° F. The animal may succumb after three or four days of fever or after a week. In rare cases recovery takes place. During the fever only several per cent. of the red corpuscles in the peripheral circulation contain parasites. There is, however, very rapid destruction going on at

* *Medical News*, December 4, 1889.

† *Transactions of the Association of American Physicians* for 1891.

the average rate of half a million of red corpuscles per cubic millimetre a day, leading in many cases to a fall from six to 1.5 million in a week. The lesions vary from case to case, depending on the duration of the disease. When the animal succumbs in the first week, the spleen is found enormously engorged, the pulp partly disintegrated. The liver is greatly enlarged, of a yellowish or saffron hue, and the bile is of the consistence of chewed grass. In sections of the fresh organ a beautiful network of bile canaliculi injected with a semisolid bile may be seen. In later stages this has disappeared, and the central portion of the lobule is now in a state of coagulation necrosis. The kidneys are enlarged, œdematous, suffused with the coloring matter of blood, and frequently the fatty tissue around them is in a state of hæmorrhagic œdema. The bladder is full of wine-red or even blackish urine. Red corpuscles are not present in it. Hæmorrhagic spots are quite common in the heart muscle, especially under the endocardium. If these various organs are examined in smear preparations, a very large number of infected corpuscles may be found in the spleen, liver, kidney, heart muscle, and plexuses of the brain. In the kidney they are largely free and resemble cocci of varying dimensions. In sections the infected corpuscles are found in the form of capillary plugs, traceable in thick sections for some distance. The parasite in the acute disease is thus largely restricted to the capillaries of the internal organs. The heart muscle has generally furnished me with the most abundant and characteristic parasites.

Starting from this acute type we may encounter all gradations down to the mildest manifestations, recognizable only by the study of the red corpuscles and the

blood count. Superficial examination may even miss the rare parasites in the peripheral circulation, but in all cases the marked fall in the number of red corpuscles and, in default of an enumeration, the characteristic basophilic substance in the red cells of oligocythemia, staining diffusely or in granules with Löffler's methylene blue, may furnish a satisfactory diagnosis. Any detailed description of the morphology of the parasite would be out of place in this paper, the more so as nothing new has been added to our knowledge since 1893. Certain statements made by Koch * concerning the earlier stages are easily harmonized with existing information. It is sufficient to state that the reproductive stage of the micro-organism has not been made out. There are several points, however, to which I should like to allude briefly. The earliest stage of intraglobular life I believe to be a motile, rodlike form of very small dimensions, whose movements within the corpuscle from one side to the other can be followed in the fresh blood.

It is not brought out by staining. In the further development of the organism, it is highly probable that there are two different modes of reproduction, similar to those first suggested by R. Pfeiffer for *Coccidium oviforme*, and recently made out by the combined labors of MacCallum, Simond, Siedlecki, Léger, and others for other sporozoa—namely, a reproductive process adapted for rapid multiplication within the host and one for an environment different from that of the host. This theory harmonizes many puzzling phenomena, among them the very rapid multiplication of the parasite in the susceptible animals leading to acute disease and the

* *Reiseberichte*, Berlin, Springer, 1898.

slow, but continuous, reproduction in the immune. None of the many animals other than cattle inoculated with infectious blood were found susceptible. The work was thereby made much more laborious and expensive.

That ticks carry the disease was suspected for many years. In 1868 Mr. John Gamgee, imported from England to study this plague for the government, wrote: "The tick theory has gained quite a renown during the past summer, but a little thought should have satisfied any one of the absurdity of the idea." When the disease was first produced near Washington by the importation of healthy North Carolina cattle, F. L. Kilborne, then superintendent of the government farm where the field experiments were conducted and in charge of the experimental animals, suggested two experiments—the infection of fields with ticks alone and the removal of ticks from Southern cattle to be penned with the natives. These were carried out and repeated during three successive seasons. They showed quite satisfactorily that the popular belief that the tick is necessary to the infection of pastures was well founded. They naturally led at first to the assumption that pastures are infected by ticks drawing the parasite with the blood, and that the native animals are infected by grazing over the infected soil, somewhat analogous to Manson's theory of the relation of mosquitoes to malaria. In order that we may understand the reasons that led to a wholly different result, a brief review of the life history of the tick is necessary. While studying this ectoparasite in 1889 I noticed that the female would lay her eggs in captivity. This fact enabled us to fill in the gaps in the life history

not easily observed in the field, and Cooper Curtice,* then helminthologist of the Department of Agriculture, studied more in detail the development of the tick by placing the young upon a heifer and watching their growth. The young six-legged arachnid, after emerging from the egg, fails to develop until placed on its special host. I have kept individuals from December to May in culture dishes without noticing any change beyond a gradual destruction due to the artificial environment. When placed on cattle, their growth begins at once, and in about a week the first moult takes place, when the animal appears provided with another pair of legs. In another week a second moult introduces the sexually mature period. Fertilization then takes place, and the female begins to swell up with the growth of eggs and the large amount of imbibed blood. After about three weeks of parasitic existence the ripe female falls to the ground, deposits one to two thousand eggs, and dies. The period of development of the embryos on the soil varies within very wide limits, depending entirely on the temperature. Fifteen days is the shortest period I have observed. After emerging from the egg, the young at once seek to attach themselves to their host and begin the life cycle anew. The age of one generation, embracing the period of incubation of the ovum and the parasitic life, averages from forty to seventy days. It will be seen from this sketch that the cattle tick is exclusively parasitic in its habits, and that it does not pass from one host to another, but completes its life upon one animal.

In the second summer season, after the pathology

* *Journal of Comparative Medicine and Veterinary Archives*, 1891 and 1892.

and parasitology of the disease and the life history of the tick had been fairly apprehended, the sudden simultaneous appearance of high fever in the animals exposed in infected fields, and the new brood of ticks upon them, forced upon me like a flash the conviction that we were here in the presence of a wholly new fact in the domain of ætiology. Everything pointed to the young tick as introducing the disease by inoculation, in spite of the newness and apparent awkwardness, as it were, of this hypothesis. Especially strong testimony in its favor was the long period of incubation. The susceptible animals penned with Southern animals or in fields infected with ticks remained absolutely well for five weeks or longer after the earliest date of field infection; then with a bound the temperature rose, and in a week the majority were dead. I ransacked the older records to obtain more evidence upon the period of incubation, but the few instances recorded confirmed our field observations. This period, it should be borne in mind, dates from the infection of the pasture and not from the date of exposure of cattle on it. The tick embryos continue their development whether cattle are present or not. After the young brood has appeared, a week or even less time suffices for the outbreak of disease. This hypothesis, that the progeny of the infected tick produces the disease, left me in doubt for a time concerning the ætiological relation of the blood parasite. Could not a poison be introduced by the young tick into the blood of cattle which destroyed certain inhibitory mechanisms, and thereby favored the multiplication of an ordinary blood parasite? This doubt was nurtured by the occasional discovery of very minute refringent bodies of varying outline within red corpuscles of susceptible

but healthy native cattle. Two lines of experiments were carried out to meet these new developments: First, the rearing of young ticks artificially in the laboratory and the infection of cattle with them; second, the transmission of the disease from one animal to another by the injection of infected blood without the intermediation of the tick. Both were successful. The first demonstrated the infectious character of the young tick, the second that the blood parasite, and not any poison introduced by the tick, is the real cause of the lesions. The disease produced directly with young ticks appeared to be somewhat less fatal than the natural exposure. This may be due to certain interferences with Nature's processes, such as the removal of female ticks before they are quite ready to drop, and the artificial incubation of the ova.

This disease may now be produced by any one, in midsummer, by sending to the permanently infected territory for ripe female ticks and incubating the eggs laid in confinement. As the disease does not spread from an inclosure, and as the ectoparasite is destroyed by frost, any danger to live stock is out of the question, if a little care is exercised. Any spot of ground once infected may remain so during the warm season, owing to the persistent vitality of the young tick until frost comes. The disease may in this way be exploited, if sufficient means are at hand, in the interest of a broader ætiology and pathology than that fostered for the promotion of agriculture by our national government. I would warn any one, however, against the danger of drawing conclusions from the study of too few cases. The wide range of pathological changes in the blood and tissues and the variable degree of blood infection

should always be borne clearly in mind. The life of the blood parasite in the tick has not yet been elucidated. It seems most in harmony with biological science to assume that the ova become infected, and that in the young tick certain organs analogous to salivary glands, connected with the operation of drawing blood, discharge the parasite into the blood of the host.

Since the ætiology of the American disease has been cleared up the same malady has been found to exist in Finland, Roumania, Italy, Australia, South Africa, and German East Africa. It will probably be found in other similarly situated countries whenever a migration of cattle shall have taken place which will tend to mingle immune and susceptible animals. It is strange that so little attention has hitherto been given by others to the transmission of the disease. Koch showed his unusual sagacity in seizing upon this one feature of the ætiology and investigating it to satisfy himself. Undoubtedly the fairy-story element about the transmission of the disease by the progeny of the infected ectoparasite, as Koch himself expresses it, led the various observers to take the position of John Gamgee, that "a little thought should have satisfied any one of the absurdity of the idea."

There are several phases of this remarkable disease which have a very important bearing upon ætiological studies of malaria; to these I wish to allude briefly before concluding. The persistence of the parasite of Texas fever in the blood after recovery, and for years after the immune Southern animal has left the enzootic territory,* shows that a kind of symbiosis has been es-

* *Bulletin No. 3, Bureau of Animal Industry, Washington, 1893, pp. 67-73.*

tablished between host and parasite. This symbiosis begins early in the life of the Southern cattle with perhaps several mild attacks of fever, and thereafter, though they remain well, they are nevertheless the carriers of a fatal infection for the non-immune Northern cattle. Their blood produces the acute type of Texas fever when injected under the skin.* This fact I regard as next in importance to the demonstration of the transmission of infection by the offspring of ectoparasites, because it proves that the blood parasite of Texas fever may exist for some time independent of the tick. Whether, under such conditions, in the course of time it may lose the power of existing in the body of the cattle tick, and thereby become non-transmissible excepting by direct inoculation, is quite within the domain of probability.† Another important fact determined by these investigations is the acquisition of immunity toward protozoan diseases. This was so thoroughly demonstrated that I need not dwell on it here. A high degree of immunity is not so easily acquired, however, as Koch's recent statements would lead us to suppose. I am inclined to believe, after a careful study of his experiment, that he was dealing with animals already endowed with considerable resistance. We know from the various researches on bacterial immunity that a partly immune animal becomes highly resistant after but little treatment. A very interesting clinical confirmation of the capacity of animals toward the acqui-

* The persistence of the blood parasite in highly immune cattle and the infectious character of their blood must be rather discouraging to those who look forward to a malarial antitoxine.

† For an analogous problem in the life of *Anguillula intestinalis*, see Leichtenstern, *Centralblatt f. Bacteriologie*, vol. xxv, 1899, p. 226.

sition of immunity is provided for us by the course of the disease itself. When animals are infected in the early months of summer the disease assumes the acute form, with high continued fever and rapid destruction of corpuscles. If the animal passes the first week alive it may recover. The temperature then falls and a rapid reproduction of red corpuscles takes place. Then there may be one or two very brief periods of high temperature with evident loss of red corpuscles and the transient appearance of parasites in the blood. Three to five weeks after the first attack there is ushered in a modified or mild type of the disease, not suggested by any outward signs of disease, but recognizable by a higher evening temperature, by persistent anæmia, and by the appearance in the peripheral circulation of large numbers of infected corpuscles. The blood parasite in this mild type or relapse appears in a form not encountered in the first acute attack. It is very small coccuslike, and situated on the periphery of the red corpuscle. These bodies, associated with very rare forms of the large pyriform bodies, may persist for four or five weeks, or until the colder weather comes. Then their disappearance ushers in the period of normal temperature and rapid rise in the number of red corpuscles. This type of fever is common in the fall, the acute stage preceding it being short and frequently not noticed. I have interpreted the peculiar features of this mild type or relapse as a resultant of partial, acquired immunity, in virtue of which the development of the blood parasite is greatly retarded, and perhaps modified, and the infected corpuscle may circulate a longer time before it becomes caught as a foreign body in the capillaries of the internal organs.

These two facts, the persistence of the blood parasite and the acquisition of immunity, I have used in building up a working hypothesis in studying the dissemination of tertian malaria in Massachusetts under the direction of the State board of health since 1896. This hypothesis assumes first of all the introduction of the malarial parasite into a region in the body of human beings. If the conditions are favorable—*i. e.*, if the infected individuals live near standing water to which mosquitoes may speedily repair and lay their eggs, and if individuals are readily accessible to the young brood for infection—the disease is likely to take root and become endemic. The blood parasite is protected over winter in the body of the infected human being. The larger the number of these, the more difficult the eradication of the disease will become unless the insects are suppressed. The harmlessness of mosquitoes in regions still free from malaria is a well-established fact. Whether they can perpetuate their own infectiousness, either by transmission of the sporozoa from brood to brood or by using some susceptible animal as host, the future must settle with the other factors of the problem. Experiments with ticks point to a loss of infectious power when they are restricted to Northern animals, but no absolute proof of this has yet been published. The appearance of malaria during the work of excavation I attribute first to the introduction of the blood parasite into the bodies of chronically infected workmen, and secondly to the accessibility of these to the insects, owing to the favorable conditions usually created during such work for breeding and for stinging the unprotected workmen. This hypothesis embraces all those conditions and phenomena regarded as neces-

sary by older theories, but it interprets them differently. It is based wholly on analogy with Texas fever.

The assumption that attacks of malarial disease beget immunity is not at all weakened by the occurrence of relapses. It should be remembered that the quinine treatment interferes with the immunizing process. In the second place, relapses may simply mean a temporary interference with the protective mechanism, a congestion or temporary stagnation of the blood somewhere which enables the parasite to get at the red corpuscles in defiance, perhaps, of the leucocytes for the time being. It is along such lines of reasoning that we can explain the attachment of the South to the hydric theory of malaria. The bad ground water produces digestive derangements in individuals already infected, and an attack of malaria is called forth. That the human beings of warm climates may not harbor malarial parasites as universally as their cattle do the Texas fever organism remains to be seen.*

The clinical expression of acquired immunity does not seem to have been studied, but it deserves attention and may lead to valuable results. Certainly the analogous conditions in the cattle malaria cited above should stimulate such studies. In the examination of blood films from cases of tertian malaria occurring in a town which has been infected with it for a number of years, it has seemed to me as if in the repeated attacks of permanent infections the parasites were so scarce in the pe-

* In a recent article (*Yearbook of the Department of Agriculture*, 1898, p. 466) Norgaard cites facts which show that Texas fever in a fatal form may be developed in apparently immune cattle by sudden extreme changes of temperature and by treating them with oil to remove the ticks.

ripheral circulation that they could not be found, although the physician who has had much experience feels positive of the character of the disease. Here we are confronted by the probability that the parasites, frequently so abundant in the peripheral circulation, are gradually confined by the growth of immunity to some restricted territory representing the *locus minoris resistentiæ* during derangements of health.

The recent investigations of Ross, confirmed and materially extended by Koch and his colleagues,* showing that in the *Proteosoma* infection of certain birds the blood parasite completes its cycle of development in one and the same insect by reappearing finally in the salivary glands, so that the insect becomes infectious a certain number of days after drawing infected blood, introduces a most interesting modification of the course pursued by the blood parasite in Texas fever. In the insect the absorption and dispensing of the infection is made possible by the powers of locomotion. In the obligatory parasitism of the tick the only mode of transmission possible is through the following generation. Evidently the former is the earlier process, the latter the modification which became established during the evolution of obligatory parasitism in the cattle tick. If the life cycle of the malaria parasite should be found the same as that of the *Proteosoma* of birds, the hypothesis of the transmission of the blood parasite to the immediate progeny of the infected mosquitoes need not be abandoned unless demonstrated to be false. In my field observations the peculiar distribution of cases of tertian fever in a newly infected territory seemed to point to the scattering of an infected brood rather than to

* *Deutsche medicinische Wochenschrift*, 1899, February 2.

the direct transmission from one individual to another. Both modes of dissemination may eventually be found in use.

In presenting these hypotheses I must beg your indulgence, for, setting aside certain very important exceptions, the making of hypotheses is usually a less arduous task than the process of demonstrating their truth. However, I am strongly convinced that the time has come for public health authorities to take some definite stand on this matter of the spreading of tertian malaria in our own climate. The eradication of this and severer forms from the tropical colonial possessions of northern nations may be destined to remain a pious wish, and the exploiting of the natives and their induction into the advantages of our social and political organization may have to be left, as heretofore, to a few hardy pioneers, or to "immunes." At any rate, this is the only comfort we can get from Nature herself just at present. In our own climate, however, it is not too late to stay the diffusion of malaria, and vigorous efforts to that end should be made, both by popular instruction and with the help of sanitary engineering. Much of the evil which manifests itself in the increasing prevalence of the mosquito is due to the carelessness and indifference of private persons, corporations, and even public authorities, who create and perpetuate the conditions which favor the silting up and the partial drying up of our streams and smaller water courses and the stagnation of surface water. The inoculation theory of malaria is a safe one with which to begin the warfare against this disease, as it has the support of analogy, of partial demonstration, and of almost all the older theories.

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